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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/060,759	01/30/2002	Adam Lerner	701586-050174-DIV-RCE	8480

50607 7590 01/06/2010

RONALD I. EISENSTEIN
100 SUMMER STREET
NIXON PEABODY LLP
BOSTON, MA 02110

EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
01/06/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/060,759	LERNER, ADAM	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,15 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *15* is/are allowed.

6)☒ Claim(s) *1-7 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 9/25/2009, are acknowledged and entered. Claims 1-7 and 15-16 are pending and under examination.

Response to Arguments

Applicants' arguments, filed 9/25/2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

As discussed in the personal interview held September 17, 2009, Fowler et al. is not available as prior art against the instant claims. Accordingly, the 35 U.S.C. 103 rejections set forth in the previous Office Action are hereby **withdrawn**.

The only remaining rejection against pending claims 1-7 and 16 is a 35 U.S.C. 112, 1st Paragraph rejection (Written Description) with respect to the claimed "...an inhibitor that specifically inhibits enzyme activity of Type 4 cyclic adenosine monophosphate phosphodiesterases...". Applicants traverse this rejection.

Applicant's arguments have been carefully considered but are not persuasive that Applicant has provided adequate written description for the claimed inhibitors. Applicant argues that while claims are read broadly before the PTO, the claims must be given a broadest reasonable interpretation and that such interpretation must be given in light of the specification as it would be interpreted by one of ordinary skill in the art. Applicant argues that one of ordinary skill in the art would interpret the claims to be directed to using specific small molecules that function similarly to rolipram and XX5 PDE4 enzyme inhibitors. Moreover, Applicant argues that the specification teaches that the claims require that these inhibitors inhibit the activity of the PDE4.

In response to the above arguments, the Examiner can find no teachings in the instant specification that limit the claimed inhibitors to small molecules. One skilled in the art would reasonably interpret "an inhibitor" to be any "pharmaceutical agent" that inhibits PDE4, not only small molecules. For example, antibodies are often used to inhibit enzymes and are reasonably pharmaceutical agents. As such, the Examiner is not persuaded that the claims are limited to small molecule inhibitors of PDE4 as asserted by Applicant.

With respect to the Examiner's position that Applicants have not provided evidence that PDE4 specific inhibitors known in the art do not inhibit PDE3 and PDE1, Applicants submit that Dr. Lerner's 3rd declaration specifically addressed this issue. In summary, Dr. Lerner pointed to examples, such as at least two different articles showing that the specific PDE4 inhibitors were known in the art to be PDE4 specific and did not inhibit, for example, PDE3 or PDE1. For example, in paragraph 16, Dr. Lerner explained that Trifilieff's (Exhibit J) data also unequivocally confirms PDE4 specificity of four different "specific" PDE4 inhibitors, including NVP-ABE171, Ariflo, Vl1294A and LAS 31025, and referring to Table 1 at page 243, Id., data showing effect on PDE4, and effect on PDE1, PDE2, PDE3 and PDE5. In paragraph 17, Dr. Lerner pointed to an article by Aoki et al. (Exhibit K) which also confirms that specific PDE4 inhibitors YM976, Rolipram, RP73401, SB207499, and CDP840 also had no effect on PDE1, PDE2, PDE3 or PDE5 referring to Table 1. This was contrasted with a compound, such as theophylline which affects PDE4 but also other PDEs.

Applicant's definition of specific PDE4 inhibitors, as set forth in the instant specification, is pertinent to the present discussion and is therefore repeated below:

> "As used herein, the phrase "an inhibitor that specifically inhibits Type 4 cyclic adenosine monophosphate phosphodiesterase" refers to a compound that inhibits Type 4 but not Type 1 or 3 phosphodiesterases. Of course, background level inhibition of Type 1 or 3 phosphodiesterases is permitted within the definition. Where the inhibitor inhibits Type 4 as well as Type 1 and/or 3, but inhibits Type 4 to a greater extent (the amounts being subject to quantitative determination by assays described herein), the phrase "preferentially inhibits Type 4 phosphodiesterases" is used herein (as distinct from "Type 4 specific." --- page 4, lines 6-13 of instant specification.

Applicant's definition of inhibitors that "specifically" inhibit PDE4 has two possible criteria. One, the inhibitor inhibits PDE4 but <u>not</u> PDE1 or PDE3. This criterion requires that absolutely <u>no inhibition whatsoever</u> of PDE1 or PDE3 can occur. Alternatively, Applicant's definition of a

specific inhibitor of PDE4 allows for "background level inhibition" of PDE1 or PDE3. Nowhere does Applicant define to what extent inhibition of PDE1 and/or PDE3 is considered to be "background level" inhibition versus inhibition. Applicant clearly distinguishes between a "specific" inhibitor of PDE4 and a preferential inhibitor of PDE4. In this regard, Applicant states that if an inhibitor inhibits PDE4 as well as PDE1 and/or PDE3, but inhibits PDE4 to a greater extent, the phrase "preferentially inhibits" PDE4 will be used, as distinct from "Type 4 specific". It is not at all clear from Applicant's definition to what extent an inhibitor can inhibit PDE1 and/or PDE3 and still be considered a "specific" versus a *preferential* or *selective* inhibitor of PDE4.

Turning now to the Trifilieff reference cited in the 3rd Lerner Declaration filed 1/16/2009, The Examiner is persuaded that the compounds NVP-ABE171, Ariflo, Vl1294A and LAS 31025 do not inhibit PDE1 or PDE3. This is based primarily on the statement of Trifilieff et al., "None of the compounds were active on all the other PDEs tested (i.e., PDE1, 2, 3, and 5)" (page 243, right column, "Inhibition of Purified PDE Isozymes").

However, Aoki et al., cited in the 3rd Lerner Declaration, teaches an inhibitor of PDE4 and compares this inhibitor with other related compounds. In Table 1, IC50 values for the inhibitors against PDE4, PDE1, PDE2, PDE3, and PDE5 are provided. It is apparent from this data that all of the inhibitors inhibit PDE1, PDE2, PDE3, and PDE5 to some extent and thus do not meet Applicant's first criteria of a "specific" inhibitor, i.e., that does not inhibit PDE1 or PDE3. The IC50 values for the tested inhibitors against PDE1, PDE2, PDE3, and PDE5 range from ">1" to ">300" μM. While Applicant's second criteria for a "specific" PDE4 inhibitor allows for "background level" inhibition of PDE1 or PDE3, because no definition of "background level" is provided, it is not apparent that an IC50 of >3 or >100 μM is only "background level" inhibition. As such, the Examiner is not persuaded that Aoki et al. provides examples of "specific" PDE4 inhibitors that meet Applicant's definition of such.

With further regard to "background level inhibition", Applicants reiterate the comments of Dr. Lerner made during the interview that a skilled artisan would know in clinical context what background level inhibition is. The Examiner is not persuaded by this argument because

Applicants have provided no factual evidence to support the assertion that a skilled artisan "would know" what Applicant means by "background level inhibition".

Applicants further argue that the industry determines the specificity of PDE4 inhibitors using comparison to known specific PDE4 inhibitors and that Applicant has taught that non-specific inhibitors such as theophylline are not contemplated in the methods (page 7, lines 10-13). The Examiner does not dispute that one skilled in the art could use known methods to determine the specificity of a compound for PDE4. However, requiring one skilled in the art to carry out random hit-or-miss testing of pharmaceutical agents to determine which agents **meet Applicant's definition of a specific PDE4 inhibitor** is indicative that Applicants were not in possession of the broadly claimed methods of use at the time the invention was filed.

In summary, Applicant's arguments and evidence are persuasive that selective or preferential PDE4 inhibitors were known in the art at the time of the invention. However, the Examiner is not persuaded that the genus of pharmaceutical agents that meet Applicant's definition of specific PDE4 inhibitors was known in the art.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 16 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to a method comprising administering to a subject a therapeutically effective amount of an inhibitor that specifically inhibits enzyme activity of Type 4 cyclic adenosine monophosphate phosphodiesterases.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims are drawn to a generic genus, *i.e.*, a method of treating CLL with an inhibitor of PDE4.

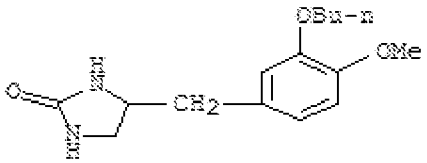
To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(i), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

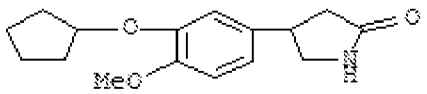
Accordingly, the courts have repeatedly held that description of a genus defined only by functional activity does not provide adequate written description of the genus unless accompanied by disclosure of structural features common to members of the genus and/or by

disclosure of a representative number of species falling within the scope of the genus. The Examiner respectfully submits that Applicant fails to disclose structural features common to members of the claimed genus and/or a representative number of species falling within the scope of the claimed genus.

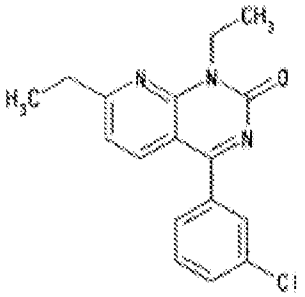
There are **two** species of the claimed genus disclosed that are within the scope of the claimed genus, *i.e.* rolipram and XX5 (page 5, lines 2-9). The disclosure of a single disclosed species (or two species) may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claims encompass numerous species that are not further described. There do not appear to be any structural features common to the claimed genus of inhibitors that specifically inhibit type 4 PDE. Structures of some type 4 PDE inhibitors are shown below.



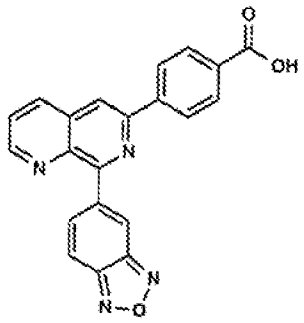
XX5, RO-1724 (disclosed by Applicants)



Rolipram (disclosed by Applicants)



YM976 (Aoki et al.)



NVP-ABE171 (Trifilieff et al.)

Clearly, Applicants recitation of rolipram and XX5 fail to disclose structural features common to members of the genus and are not a representative number of species falling within the disclosed genus.

Applicants explicitly define the term "an inhibitor that specifically inhibits Type 4 cyclic adenosine monophosphate phosphodiesterase" as a compound that inhibits Type 4 but **not** Type 1 or 3 phosphodiesterases (page 4, lines 6-8). However, Applicants additionally state that "background level inhibition of Type 1 or 3 phosphodiesterases is permitted within the definition" (*id.* at lines 8-9). While no definition of "background level inhibition" is provided by Applicants, Applicants do state that where an inhibitor inhibits Type 4 as well as Type 1 and/or 3, but inhibits Type 4 to a greater extent, the phrase "*preferentially* inhibits Type 4 phosphodiesterases" is used herein (as distinct from "Type 4 specific"). To what extent the Type 4 inhibition has to be "greater" than Type 1 and/or 3 inhibition to constitute preferential versus specific inhibition is not disclosed in the specification (*i.e.*, Applicants have not described what constitutes background level inhibition versus what constitutes preferential inhibition). For example, would a compound that inhibits Type 4 PDE with an IC_{50} of 10 nM and Type 1 PDE with an IC_{50} of 1 μM be considered a "preferential" inhibitor of Type 4 PDE or a "specific" inhibitor of Type 4 PDE? The compound clearly *inhibits* Type 1 PDE and thus does not appear to fall within Applicant's definition of **not** inhibiting Type 1 or 3 PDE. Alternatively, Applicant could consider the inhibition of Type 1 PDE to be "background level inhibition".

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is a method of treating CLL with a generic genus of inhibitor compounds, *i.e.*, specific inhibitors of Type 4 PDE

purported to have activity in treating chronic myelogenous leukemia. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Allowable Subject Matter

Claim 15 is allowed.

The following is a statement of reasons for the indication of allowable subject matter: The prior art does not teach or fairly suggest treating chronic lymphocytic leukemia with 4-(3-Butoxy-4-methoxybenzyl)-2-imidazolidinone.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614